HEREDITARY ARRHYTHMIA CORNER: LEARNING FROM CHALLENGING PATIENTS

An Adolescent with Possible Arrhythmogenic Right Ventricular Dysplasia and Long QT Syndrome: Evaluation and Management

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We describe a unique presentation of arrhythmogenic right ventricular dysplasia (ARVD) in a 14-year-old Caucasian male who was additionally diagnosed with long QT syndrome (LQTS). Genetic testing eventually confirmed the diagnosis of both ARVD and LQTS, which combined, to our knowledge, has not been reported in the literature.

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CASE PRESENTATION

The patient is a previously healthy 14-year-old male who was involved in high demand athletics. Following a football practice, he felt very fatigued and proceeded to take a 5-hour rest. His primary care physician noticed an irregular heart rate at the time of a preparticipation sports examination months prior to initial presentation. His mother astutely assessed his pulse rate as irregular at the time of his unusual fatigue. Due to these findings, he was taken to a local Emergency Department where an electrocardiogram (ECG) (Mac 5500 ECG Diagnosis System, General Electric, Friburg, Germany) revealed frequent premature ventricular complexes (PVC)s. Subsequently, he was referred to our clinic for further evaluation. At the time of his initial assessment, he was otherwise asymptomatic from a cardiovascular perspective and denied any preceding illnesses. His family history was significant for distant maternal cousin that required an unknown type of "heart surgery"

at the age 18. A maternal grandmother that was receiving beta-blocker therapy and had an artificial pacemaker placed due to a "rhythm abnormality." A paternal uncle developed atrial fibrillation at the age of 20. Several paternal male relatives died from a heart-related death in their early fifties. There were no other sudden, unexplained deaths in the family.

At his initial evaluation, his cardiac auscultatory examination was within normal limits without an irregular rhythm. He had an ECG performed that revealed a normal sinus rhythm with a ventricular rate of 74 beats per minute (BPM). There was no evidence of ventricular ectopy, but his QTc interval was mildly prolonged at 460 ms. A complete two-dimensional echocardiogram (iE33, Philips, Bothell, WA, USA) revealed normal left ventricular systolic function with an echo-bright (6 mm × 26 mm) mass within the interventricular septum.

An exercise stress test using the Bruce protocol was performed. The patient was able to exercise for 12 minutes and 37 seconds achieving 12.8

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Figure 1. Four-chamber view of the MRI showing dyskinesia of the RV free wall with associated fibrofatty infiltration and possible delayed enhancement of the RV free wall.

METS. There was no ventricular ectopy at rest or during peak exercise. However, seven minutes into recovery frequent polymorphic PVCs of left bundle branch (LBBB) and right bundle branch (RBBB) morphology, both with superior axis, appeared. A 24-hour Holter monitor that was previously

recoded at an outside institution was reviewed. The Holter revealed frequent (20%) PVCs of two different morphologies, presented isolated and in couplets. There was a 5 beat run of nonsustained ventricular tachycardia (VT) after exercise. Signal average ECG was performed, and there was no evidence of abnormal late potentials. Standard QRS duration was 108 ms and filtered QRS duration was 117 ms; the filtered QRS duration met minor criteria of depolarization/conduction abnormality based on patient's gender and body surface area (BSA). Cardiac MRI (Avanto 1.5, Siemens, Erlangen, Germany) revealed signal abnormality and abnormal enhancement along the right aspect of the intraventricular septum, which appeared to extend into the right ventricular outflow tract (Figure 1). The final read was significant for: (1) severe dyskinesia of the right ventricular (RV) free wall with associated fibro-fatty infiltration and possible delayed enhancement of the RV free wall, (2) moderate RV dysfunction with an ejection fraction (EF) of 32%, and (3) evidence of focal dyskinesia at the left ventricular lateral wall toward the apex where appeared to be a fibro-fatty infiltration.

A repeat ECG revealed inverted T waves in lead V₁ and V₂, PVCs of different morphology and a QTc of 497 ms (Figure 2). Due to consistently prolonged QTc a diagnosis of long QT syndrome (LQTS) was considered. According to the Schwartz criteria the patient had 3 points based off his QTc of 497ms [3].

Figure 2. Twelve-lead ECG recorded on September 11, 2009. There is sinus rhythm with frequent late-coupled premature ventricular complexes, with variation in the morphology of the premature ventricular complexes in the lead II rhythm strip (second complex vs. ninth and eleventh complexes). The T waves of the sinus conducted beats have normal configuration with QT-II = 0.40 s, RR = 0.76 s, and QTc = 0.46 s; the T waves of the sinus conducted beats are not inverted in V₂ or V₃.

Furthermore, he had 2 major and 2 minor criteria for diagnosis of arrhythmogenic right ventricular dysplasia (ARVD) based on Revised Task Force Criteria. The two major criteria were nonsustained VT of LBBB morphology with a superior axis and the MRI findings of regional RV dyskinesia and RVEF less than 35%. The two minor criteria were inverted T waves present in lead V₁ and V₂ and the filtered QRS duration >114 ms on signal average ECG.

Cardiac catheterization followed in order to assess hemodynamic parameters, obtain an endomyocardial biopsy, and carry out a full electrophysiology (EP) study with possible ablation. The cardiac catheterization revealed normal baseline hemodynamic parameters, normal coronary artery distribution, and right ventricular hypertrophy with dyskinesia of the right ventricular apex. The left ventricular size and systolic function were normal. Right ventricular (septal) endomyocardial biopsy demonstrated moderate myocyte hypertrophy with 30% fibrosis but without evidence of adipocyte infiltration. Additionally, there was no evidence of inflammation or viral inclusions. During the EP study there was easily inducible and reproducible nonsustained VT (cycle length of 240 ms). VT was of LBBB morphology, positive in lead II, lead III, and aVF with S:R transition from V₅ to V₆. The inducible VT morphology was identical to the morphology of clinical VT. The longest VT duration was 40 seconds under general anesthesia. Mapping was performed during tachycardia. Successful ablation terminated tachycardia at the anterolateral RV wall. There were only isolated PVCs of RBBB morphology following the ablation. The morphology was different when compared to clinical RBBB PVCs. Voltage mapping of the RV was performed. There were patchy regions with dense scars and voltages less than 0.5 mV along the right ventricular outflow tract region, at the anterolateral RV wall, and at the right ventricular base posterolateral to the tricuspid valve.

Following the procedure he was hospitalized for initiation of sotalol therapy. The therapy was titrated up to 120 mg twice a day. The initiation of sotalol decreased the degree of isolated ectopy and mildly prolonged QTc to 490 ms. Genetic analysis revealed that the patient was heterozygous for a known disease-causing mutation, Arg328Cys (c.982C>T), in the cardiac potassium voltage-gated channel type H2 (KCNH2) gene, consistent with an autosomal dominant form of LQTS. The patient

was heterozygous for a presumed pathogenic mutation in c.148 151de1ACAG(p.Thr50fs), in exon 1 of the PKP2 gene. He was also heterozygous for a variant of unknown significance, c.1901G>A (p.Arg634His), in the DSC2 gene.

These findings were consistent with causative mutations for long QT syndrome type 2 (LQT2) and ARVD. Following the genetic testing and discussion with the family patient underwent prophylactic single-chamber single-coil implantable cardioverter defibrillator (ICD) implantation.

Dr. Moss, please discuss the diagnosis and implications of the findings noted in this patient. Are there really two genetic diagnoses? What therapy would you recommend for this patient?

This 14-year-old male patient had palpitations and documented frequent PVCs, but no history of syncope and an unremarkable family history. On the ECG dated Sept. 11, 2009 (Fig. 2), there is sinus rhythm with frequent late-coupled PVCs, with slight variation in the morphology of the PVCs in the lead II rhythm strip; the T waves of the sinus conducted beats have normal configuration with QT-II = 0.40 seconds, RR = 0.76 seconds, and QTc = 0.46 seconds. The T wave is inverted only in V₁, but does not extend to V₂ and V₃. An MRI was interpreted as consistent with ARVD. Genetic testing revealed an LQTS mutation (Arg328Cys) in the HERG-LQT2 (KCNH2) gene and a mutation in the plakophilin-2 gene that has been associated with, but is not specific for, ARVD.

The concern is whether this patient is at risk for sudden arrhythmogenic cardiac death, and if so, what preventive therapy is indicated.

Although there is an LQT2 mutation in this patient, the mutation has been reported in only 4 patients and is located in the N-terminus of the membrane spanning protein.¹ In my opinion, the clinical, ECG, and mutation-location findings suggest that this patient is a low-risk for LQTS-related life-threatening arrhythmias, especially with the absence of syncope and a QTc<500 ms.

The diagnosis of ARVD is equivocal. The ECG T-waves are not inverted in V₁-V₃/V₄ and the overall ECG pattern does not suggest ARVD. The error rate in diagnosing ARVD by MRI is high, even when experts in the field are involved in image interpretation. The right ventricular biopsy was also not diagnostic of this disorder. A plakophilin-2 gene mutation reported in this

patient is a presumed pathogenic mutation, but not all plakophilin-2 gene mutations cause ARVD.²

Because the patient was thought to have possibly two different genetic-related arrhythmogenic disorders, the patient underwent extensive invasive studies including cardiac catheterization, electrophysiologic testing, and radiofrequency ablation of a suspect VPC focus. If the physicians thought the patient had LQTS, antiarrhythmic therapy with sotalol with its known QT prolonging effect might add more risk than benefit.

On the basis of the findings presented in the case report, I do not think this patient is at high risk for sudden cardiac death. I would have initiated beta-blocker therapy with repeat exercise testing and a 48-hour Holter recording. Outpatient observation involving follow-up clinical evaluation and repeat ECGs over several months are indicated for they would provide a better evaluation of the clinical disorder and the frequency and complexity of the PVCs. I would not have initiated therapy with an ICD on the basis of the available clinical, electrocardiographic, and genetic information, but would consider it an option if the subsequent clinical course reveals unstable ventricular tachyarrhythmias.

EDITORIAL COMMENTS

As in other clinical tests, genetic analyses are to be judiciously assessed with proper clinical astuteness. We are beginning to learn conditions such as arrhythmogenic right ventricular cardiomyopathy

or dysplasia may be a spectrum of diseases affecting the right ventricle as well as other aspects of the heart. To establish a diagnosis at early stages of the disease can be challenging and complex, as attested by the arduous diagnostic criteria set forth by the Task Force.³ Furthermore, familiarization of specific genetic testing results in the setting of previously reported cases may provide an important background for the interpretation of results. Sometimes, even with the best effort and care, clinical test results can be complex and difficult to interpret, as in this case.

We as clinicians need to always be cognizant that a hereditary arrhythmia diagnosis impacts beyond the treatment of the presenting patient; lifelong activities and concerns for the rest of the family members may all be transformed as well. As in all patients with suspected hereditary arrhythmia, this unusual case serves to once again, with a different angle, illustrate the importance of correlating phenotypic manifestations and genotypic information.

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